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SHORT COMMUNICATION

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Biomimetic Three-Component Assembly of the Central Core of Halichonadins K and L

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The one-step cascade assembly of the central core of halichonadins K and L, two dimeric sesquiterpenoids of marine origin, is described for a model system providing suitable conditions towards the total synthesis of the two molecules. A biomimetic multicomponent reaction involving a glycine, a C_5 unit presumably derived from lysine, and an isocyanide mimic of the terpene decalins is studied.

Introduction

Halichonadins K and L (**1** and **2**, Figure 1), recently isolated from a marine sponge *Halichondria* sp., are striking new dimeric terpenoids.[1] In fact, two sesquiterpenic decalins are linked through an unusual piperidine ring in the way that this latter is (1) *N*-substituted by an amino acid chain, (2) hydroxylated at the 4-position, and finally and most importantly (3) substituted by two amide functions that bear the decalins at the 2,6-positions in a *cis* configuration.

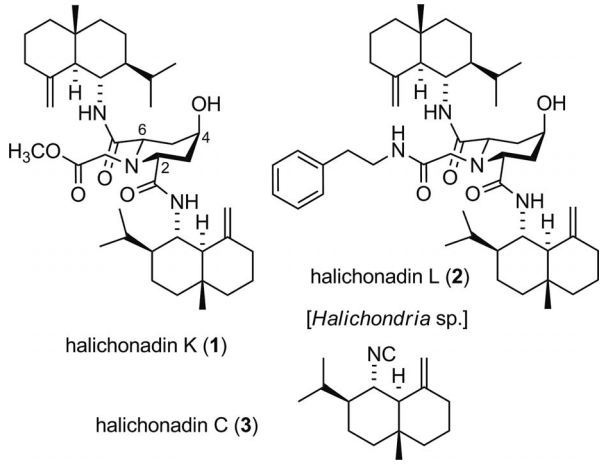

Figure 1. Structures of halichonadins K, L, and C (**1**–**3**).

In terms of biosynthesis, whereas the terpenic decalin substructures are of the classical eudesmane type, the puzzling origin of the central core caught our attention. Knowing the existence of halichonadin C[2] (**3**, Figure 1), which strictly corresponds to the decalin part of **1** and **2** but flanked by an isocyanide functional group,[3,4] the assembly may, in principle, be explained by a Strecker-type reaction followed by hydrolysis into the amide (vide infra). It is then plausible to trace back (Figure 2), besides the two halichonadin C units, a hydroxylated C_5 unit, which could presumably be derived from L-lysine (**4**), and a C_2 or C_2/C_2-C_6N-substituents (in the case of **1** or **2**, respectively), which could find their origin in glyoxylic acid (**5**) and L-phenylalanine (**6**).

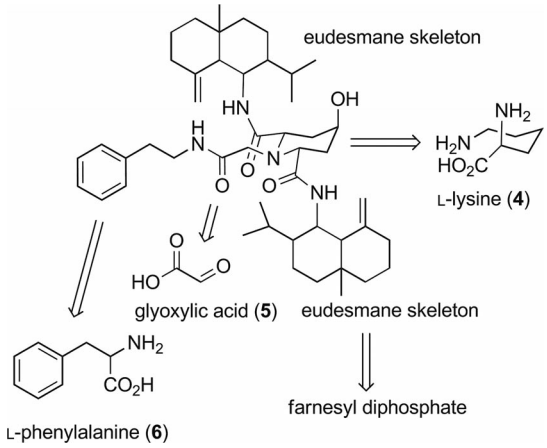

Figure 2. Plausible biosynthetic building blocks of halichonadins K, L, and C (**1**–**3**).

In agreement with Kobayashi's proposal,[1] we herein give a full mechanistic hypothesis towards **1** and **2** as represented in Scheme 1. A central dihydropyridinium salt such as **7** (that may arise from classical biochemical transformations from L-lysine and glyoxylic acid) could be considered as a central electrophilic intermediate permitting the assembly of the different parts of **1** and **2**. The mechanism involved in the particular formation of the amidic lateral substituents is highlighted in Scheme 1 and is reminiscent of that of

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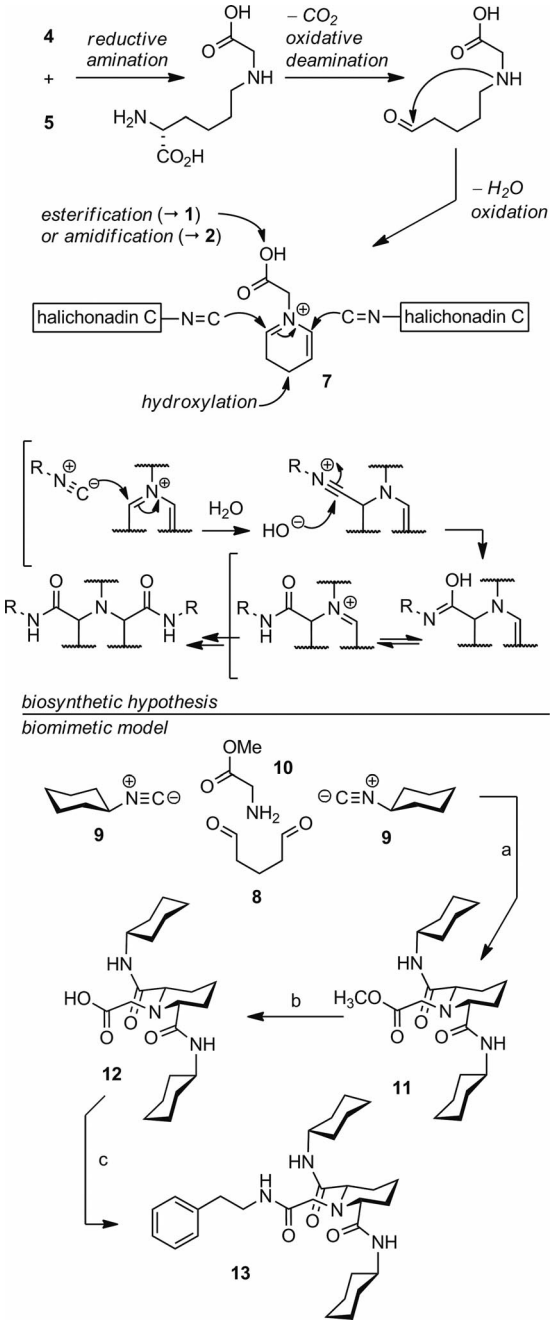
known multicomponent reactions of the Ugi type.[5] The nucleophilic attack of the isocyanide onto the iminium salt followed by hydrolysis of the nitrilium intermediate could, in that way, explain the formation of the amides of halichonadins K and L. In view of this plausible and detailed biosynthetic scenario, our interest in biomimetic syntheses in the field of natural product synthesis prompted us to investigate the assembly of the central core of these intriguing new natural substances.



Scheme 1. Detailed biosynthetic scenario towards halichonadins K, L, and C (**1–3**) and biomimetic multicomponent model reaction. Reagents and conditions: (a) MeOH/4% citric acid in H_2O, **10** + **8** (1.2 equiv.), r.t., 3 min, then **9** (2 equiv.), 48 h, r.t. (36%); (b) MeOH/KOH in H_2O, r.t., 12 h (84%); (c) 2-phenylethylamine (1 equiv.), EDC (1.2 equiv.), HOBt (1.2 equiv.), CH_3CN, 12 h, r.t. (61%).

Results and Discussion

Glutaraldehyde (**8**), a C_5 dialdehyde, is an ideal biomimetic equivalent of L-lysine[6] when dihydropyridinium salt intermediates are postulated, as is the present case with postulated intermediate **7**. Thus, glutaraldehyde (which provides the presumably lysine-derived C_5 unit), cyclohexane isocyanide (**9**, as a convenient surrogate of the terpene moiety), and glycine methyl ester (**10**) were chosen for the study of the one-step three-component assembly of the central core of **1** and **2**. The mixture of the units was studied, and in MeOH/H_2O a satisfactory 36% yield of new compound **11** was observed. Indeed, the reaction between **8** and **10** permits access to a reactive dihydropyridinium salt that is related to postulated **7**, which then undergo two stabilizing nucleophilic attacks from **9**.[7] Structure elucidation revealed the awaited formation of the multicomponent reaction adduct corresponding to the central core of **1** obtained as a single *cis*-diastereomer, as ascertained by NMR spectroscopy. Following Kobayashi's strategy for the correlation between **1** and **2**, model compound **11** was hydrolyzed into corresponding acid **12** and finally converted by esterification under classical coupling conditions [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and *N*-hydroxybenzotriazole (HOBt)] into **13**, which corresponds to an advanced biomimetic model for halichonadin L (**2**). Analysis of compounds **11** and **13** by NMR spectroscopy was in agreement with the data available for **1** and **2**. Specifically, identical chemical shifts for the CH protons at the 2,6-positions of the piperidine ring allowed the relative *cis* configuration to be ascertained [**11**: $\delta(^1H)$ = 4.15 ppm, $\delta(^{13}C)$ = 62.3 ppm; **13**: $\delta(^1H)$ = 4.21 ppm, $\delta(^{13}C)$ = 61.9 ppm, see the Experimental Section for details].

Conclusions

We have set the stage and provided optimized experimental conditions for the biomimetic assembly of the central core of original halichonadins K and L, which thereby reinforces its proposed biosynthetic scheme. The present work also opens the way to the convergent synthesis of a large number of analogs for biological evaluation. Finally, this straightforward access to piperidine heterocycles also contributes to the long-lasting interest in cascade[8] and multicomponent[9] reactions in the field of natural product total synthesis, especially when inspired by nature biosynthetic pathways.

Experimental Section

General: Reactions were monitored by thin-layer chromatography carried out on silica gel plates (Merck TLC Silica gel 60_{F254}) by using UV light as a visualizing agent and sulfuric vanillin/heat and Draggendorff reagent/heat as developing agents. Merck Silica gel

Geduran® Si 60 (particle size 40–63 mm) and Sephadex LH-20® (Pharmacia) gels were used for column chromatography. NMR spectra were recorded in [D_5]pyridine with an AM-300 (300 MHz) or AM-400 (400 MHz) Bruker spectrometer and calibrated by using undeuterated pyridine as an internal reference. IR spectra were recorded with a Vector 22 Bruker spectrometer. Mass spectra were recorded at the "Service d'Analyse des Médicaments et des Métabolites" (Université Paris-Sud).

(*R*,*S*)-Methyl 2,6-Bis(cyclohexylcarbamoyl)piperidin-1-yl-acetate (11): To a solution of glycine methyl ester hydrochloride (500 mg, 4.0 mmol) in MeOH (5 mL) was added a 4% aqueous solution of citric acid followed by the addition of glutaraldehyde (480 mg, 4.8 mmol, 1.2 equiv., 870 μL of a 50% aqueous solution). The mixture was stirred for 3 min at room temperature and then cyclohexylisocyanide (890 μL, 8.0 mmol, 2 equiv.) was slowly added. The resulting reaction mixture was then stirred for 48 h at room temperature, diluted with H_2O (40 mL), and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 1:1 then 3:7) and by Sephadex® LH-20 column chromatography (MeOH/CH_2Cl_2, 1:1) to provide **11** as a colorless oil (588 mg, 36%). ^{1}H NMR (400 MHz, [D_5]pyridine): δ = 1.07 (m, 2 H), 1.18–1.30 (8 H), 1.43 (m, 2 H), 1.53–1.68 (4 H), 1.73 (m, 2 H), 1.82–2.04 (8 H), 3.64 (s, 3 H), 3.68 (d, J = 17.2 Hz, 1 H), 3.85 (d, J = 17.2 Hz, 1 H), 3.99 (m, 2 H), 4.15 (m, 2 H), 7.86 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D_5]): δ = 20.1, 25.5, 26.2, 28.2, 33.5, 33.6, 48.3, 52.2, 54.8, 62.3, 173.0, 173.4 ppm. IR (film): $\tilde{\nu}$ = 2950–2900, 2858, 1741, 1658, 1642, 1529, 1200 cm^{-1}. HRMS (TOF MS ES+): calcd. for $C_{22}H_{38}N_3O_4$ [M + H]$^+$ 408.2856; found 408.2863.

(*R*,*S*)-2,6-Bis(cyclohexylcarbamoyl)piperidin-1-yl-acetic Acid (12): To a solution of **11** (98 mg, 0.24 mmol) in MeOH (3 mL) was added a solution of KOH (4 M in H_2O, 3 mL), and the reaction mixture was stirred for 12 h at room temperature. The solution was then diluted with H_2O (10 mL), neutralized with 1 M aqueous HCl solution, and extracted with CH_2Cl_2 (4 × 4 mL). The combined organic extracts were then dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford compound **12** (79 mg, 84%) as a white amorphous solid. ^{1}H NMR (300 MHz, [D_5]pyridine): δ = 1.05 (m, 2 H), 1.18–1.45 (10 H), 1.52–1.70 (4 H), 1.78 (m, 2 H), 1.84–2.04 (8 H), 3.80 (d, J = 17.4 Hz, 1 H), 3.92 (d, J = 17.4 Hz, 1 H), 4.04 (m, 2 H), 4.20 (m, 2 H), 7.14 (br. s, 1 H), 8.09 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D_5]pyridine): δ = 20.5, 25.4, 26.2, 27.6, 33.5, 33.6, 48.3, 55.3, 62.4, 173.2, 175.5 ppm. IR (film): $\tilde{\nu}$ = 2950–2900, 2857, 1643, 1642, 1527, 1451 cm^{-1}. HRMS (TOF MS ES+): calcd. for $C_{21}H_{36}N_3O_4$ [M + H]$^+$ 394.2700; found 394.2704.

(*R*,*S*)-[2,6-Bis(cyclohexylcarbamoyl)piperidin-1-yl-acetyl]-(2-phenylethyl)amine (13): To a solution of **12** (65 mg, 0.17 mmol) and 2-phenylethylamine (20 mg, 0.17 mmol, 1 equiv.) in CH_3CN (4 mL) was added EDC hydrochloride (38 mg, 0.2 mmol, 1.2 equiv.), HOBt (27 mg, 0.2 mmol, 1.2 equiv.), and triethylamine (89 μL, 0.66 mmol, 3.8 equiv.). After stirring for 12 h at room temperature, the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were then dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 98:2) to provide **13** (50 mg, 61%) as an amorphous colorless solid. ^{1}H NMR (400 MHz, [D_5]pyridine): δ = 1.06 (m, 2 H), 1.17–1.37 (8 H), 1.45 (m, 2 H), 1.55–1.70 (4 H), 1.75 (m, 2 H), 1.85–2.00 (8 H), 2.88 (t, J = 7.2 Hz, 2 H), 3.67 (m, 2 H), 3.70 (m, 2 H), 4.00 (m, 2 H), 4.21 (t, J = 6 Hz, 2 H), 7.23–7.32 (5 H), 8.37 (d, J = 7.6 Hz, 2 H), 8.76 (t, J = 5.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_5]pyridine): δ = 20.2, 25.7, 26.2, 29.0, 33.6, 33.8, 36.7, 41.4, 48.6, 57.5, 61.9, 127.0, 129.2, 129.6, 140.4, 172.1, 173.6 ppm. IR (film): $\tilde{\nu}$ = 3200, 2950–2900, 2854, 1640, 1527, 1451, 1250 cm^{-1}. HRMS (TOF MS ES+): calcd. for $C_{29}H_{45}N_4O_3$ [M + H]$^+$ 497.3486; found 497.3491.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra of compounds **11**–**13**.

Acknowledgments

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